

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
SHAWNA CANNON LEMON
MYERS BIGEL SIBLEY & SAJOVEC, P.A.
P.O. BOX 37428
RALEIGH, NC 27627

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 5623.16.WO	Date of mailing (day/month/year) 14 JAN 2005
International application No. PCT/US04/18171	International filing date (day/month/year) 07 June 2004 (07.06.2004)
Applicant ENDACEA, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:
 The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35

 For more detailed instructions, see the notes on the accompanying sheet.
2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.
4. **Reminders**
 Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.
 The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.
 Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.
 In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.
 See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/ US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer

Mark D. Borch

Telephone No. (571) 272-1600

Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 5623.16.WO	FOR FURTHER ACTION <small>see Form PCT/ISA/220 as well as, where applicable, item 5 below.</small>	
International application No. PCT/US04/18171	International filing date (day/month/year) 07 June 2004 (07.06.2004)	(Earliest) Priority Date (day/month/year) 09 June 2003 (09.06.2003)
Applicant ENDACEA, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (See Box No. III)

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/18171

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(7) : C07D 473/06; A61K 31/522; A61P 9/04, 11/06, 37/08, 13/12, 25/28, 25/24, 3/04, 3/10, 29/00, 25/16
 US CL : 544/271, 272; 514/263.35; 424/9.1;

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 U.S. : 544/271, 272; 514/263.35; 424/9.1; 536/24.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 CAS Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,489,332 B1 (NEELY et al.) 03 December 2002 (03.12.2002), see all claims; paragraph bridging columns 4-5 and the following two paragraphs; column 6, lines 18-20; and synthesis at cols 6-7.	1-33

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

10 November 2004 (10.11.2004)

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
 Commissioner for Patents
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 Facsimile No. (703) 305-3230

Date of mailing of the international search report

14 JAN 2005

Authorized officer

Mark L. Berch

Telephone No. (571) 272-1600

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
SHAWNA CANNON LEMON
MYERS BIGEL SIBLEY & SAJOVEC, P.A.
P.O. BOX 37428
RALEIGH, NC 27627

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing (day/month/year) 14 JAN 2005	
FOR FURTHER ACTION See paragraph 2 below	
Applicant's or agent's file reference 5623.16.WO	
International application No. PCT/US04/18171	International filing date (day/month/year) 07 June 2004 (07.06.2004)
Priority date (day/month/year) 09 June 2003 (09.06.2003)	
International Patent Classification (IPC) or both national classification and IPC IPC(7): C07D 473/06; A61K 31/522; A61P 9/04, 11/06, 37/08, 13/12, 25/28, 25/24, 3/04, 3/10, 29/00, 25/16 and US Cl.: 544/271, 272; 514/263.35; 424/9.1;	
Applicant ENDACEA, INC.	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Mark L. Berch Telephone No. (571) 272-1600
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US04/18171

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing
☐ contained in international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US04/18171

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>1-33</u>	YES
	Claims <u>NONE</u>	NO
Inventive step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-33</u>	NO
Industrial applicability (IA)	Claims <u>1-33</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Claims 1-33 an inventive step under PCT Article 33(3) as being obvious over Neely.

The narrow claims of the reference teach, with one exception, the subject matter of claims 1-33. Probes are taught in the paragraph bridging columns 4-5 and the following two paragraphs. Pharmaceutical uses appear at column 6, lines 18-20. The sole difference is that in Neely, the R8 substituent is present at the para position, whereas in the claims, it is at the ortho or meta position (see third from last line of page 30). It is well established that position isomers are prima facie structurally obvious even in the absence of a teaching to modify. The isomer is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing the position isomers. Position isomerism has been used as a tool to obtain new and useful drugs; it is a fact of close structural similarity. With regard to the synthesis, although the claims recite the use of the acid R3COOH to do the cyclization, and the reference has the aldehyde, the aldehyde in the reference is reacted with an oxidant (e.g. NaIO₄; see column 7) which will convert the aldehyde into the acid so that the same step is actually involved.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US04/18171

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 7-28, 31 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims 7-28, 31 are indefinite for the following reason(s):

1. The nature of the "spacer" is unknown. It states where something is, but not what it is. It mentions having a "functionality which bonds..." but almost anything will bond to a N or O atom.
2. The scope of the "label" is also unclear. Without knowing what it is supposed to diagnose, it is unknown what sorts of things will qualify as labels and what will not.
3. The term "A1 adenosine receptor related disorders" recited in claim 22 is of unknown scope. This receptor is only partially understood, and one cannot be sure which disorders, if any, are definitely not within the scope of this claim.
4. AIDS is listed twice in claim 28.
5. Claim 31 is incomplete. No actual step is recited. What is the administration method? Who is in need of it?

Claims 1-30 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims 1-30 not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because: These claims call for the production of solvates and hydrates. Yet, of all the examples presented in the specification, none of them produced solvates or hydrates. These compounds appear not to form such solvates and hydrates, so how will they be prepared?

Claims 22 and 28 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims 22 and 28 not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because: The notion that A1 adenosine receptor related disorders can be treated generally with receptor antagonists has no scientific basis. Indeed, very few such disorders are currently treatable with such antagonists. Moreover, some of the disorders in claim 28 are deemed pharmaceutically untreatable at present, e.g. ARDS and SARS. Still others are not considered sufficiently A1-related, or A1 related at all, e.g. Alzheimer's Disease, Parkinson's Disease and AIDS. That is, all drugs which treat Alzheimer's Disease, Parkinson's Disease and AIDS operate by an entirely different mechanism.